

# Response Differences in Monkey TE and Perirhinal Cortex: Stimulus Association Related to Reward Schedules

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**Liu, Zheng and Barry J. Richmond.** Response differences in monkey TE and perirhinal cortex: stimulus association related to reward schedules. *J. Neurophysiol.* 83: 1677–1692, 2000. Anatomic and behavioral evidence shows that TE and perirhinal cortices are two directly connected but distinct inferior temporal areas. Despite this distinctness, physiological properties of neurons in these two areas generally have been similar with neurons in both areas showing selectivity for complex visual patterns and showing response modulations related to behavioral context in the sequential delayed match-to-sample (DMS) trials, attention, and stimulus familiarity. Here we identify physiological differences in the neuronal activity of these two areas. We recorded single neurons from area TE and perirhinal cortex while the monkeys performed a simple behavioral task using randomly interleaved visually cued reward schedules of one, two, or three DMS trials. The monkeys used the cue's relation to the reward schedule (indicated by the brightness) to adjust their behavioral performance. They performed most quickly and most accurately in trials in which reward was immediately forthcoming and progressively less well as more intermediate trials remained. Thus the monkeys appeared more motivated as they progressed through the trial schedule. Neurons in both TE and perirhinal cortex responded to both the visual cues related to the reward schedules and the stimulus patterns used in the DMS trials. As expected, neurons in both areas showed response selectivity to the DMS patterns, and significant, but small, modulations related to the behavioral context in the DMS trial. However, TE and perirhinal neurons showed strikingly different response properties. The latency distribution of perirhinal responses was centered 66 ms later than the distribution of TE responses, a larger difference than the 10–15 ms usually found in sequentially connected visual cortical areas. In TE, cue-related responses were related to the cue's brightness. In perirhinal cortex, cue-related responses were related to the trial schedules independently of the cue's brightness. For example, some perirhinal neurons responded in the first trial of any reward schedule including the one trial schedule, whereas other neurons failed to respond in the first trial but respond in the last trial of any schedule. The majority of perirhinal neurons had more complicated relations to the schedule. The cue-related activity of TE neurons is interpreted most parsimoniously as a response to the stimulus brightness, whereas the cue-related activity of perirhinal neurons is interpreted most parsimoniously as carrying associative information about the animal's progress through the reward schedule. Perirhinal cortex may be part of a system gauging the relation between work schedules and rewards.

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## INTRODUCTION

Ablation experiments in monkey have established that inferior temporal cortex is critical for normal visual pattern recog-

nition (Iwai and Mishkin 1968; Mishkin 1982; Mishkin et al. 1997). However, inferior temporal cortex is not a single homogeneous region. Electrophysiological studies so far have found that two directly connected inferior temporal areas, TE and perirhinal cortex (Saleem and Tanaka 1996; Suzuki and Amaral 1994a), are very similar in neuronal response properties despite a large body of behavioral and anatomic evidence indicating that they are distinct. In this study, we identify striking differences in the neuronal response properties between these two areas related to association of the stimulus with predictable reward schedules.

Selective ablations of TE and perirhinal cortex indicate that their roles in pattern recognition are different (Buckley et al. 1997). Removal of the perirhinal cortex impairs performance of a short-term memory task but not a color-discrimination task, whereas removal of area TE impairs performance of a fine color-discrimination task but not a short-term memory task. Anatomic evidence also indicates that these areas should be considered distinct. Area TE is connected directly with cortical area V4, whereas perirhinal cortex is not. Perirhinal cortex is connected with entorhinal cortex, whereas area TE is not (Suzuki 1996; Suzuki and Amaral 1994b; Witter 1993). Perirhinal cortex is also strongly connected to brain areas related to reward and motivation, such as ventral striatum (Van Hoesen 1981; Witter and Groenewegen 1986) and ventral tegmental region (Akil and Lewis 1993, 1994; Insausti et al. 1987), whereas area TE is not. In addition, surveys of cortex list perirhinal cortex among two or three regions with the densest distribution dopamine carrying fibers and dopamine receptors (Akil and Lewis 1993, 1994; Berger et al. 1988; Richfield et al. 1989).

Given the anatomic and behavioral results related to these two areas, it seems reasonable to expect substantial differences in signals carried by the single neurons in them. Thus far, however, physiological recordings in these two areas have found little difference between them. Neurons within both areas show great stimulus selectivity for complex visual patterns (Baylis et al. 1987; Desimone et al. 1984; Gross et al. 1972; Nakamura et al. 1994; Riches et al. 1991; Richmond and Sato 1987; Tanaka et al. 1991). In both areas, these stimulus-elicited responses are modulated by several factors, including display sequence in a delayed match-to-sample (DMS) task (Eskandar et al. 1992; Li et al. 1993; Miller et al. 1993), attention (Desimone 1996; Richmond et al. 1983), and stimulus familiarity (Gross et al. 1979; Miller et al. 1991; Riches et al. 1991).

In our search for differences in the neuronal response properties between these two areas, two observations influenced us:

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the connection of perirhinal cortex, but not area TE, to the ventral striatum (Van Hoesen 1981; Witter and Groenewegen 1986) where neurons carry information about reward and motivation (Apicella et al. 1991; Bowman et al. 1996; Schultz et al. 1992; Shidara et al. 1998; Williams et al. 1993) and the structurally organized and dense dopamine carrying fibers and dopamine receptors in perirhinal cortex (Akil and Lewis 1993, 1994; Berger et al. 1988; Richfield et al. 1989). Dopamine is thought to play a central role in signaling reward (Schultz 1997, 1998). We hypothesized that the responses of perirhinal neurons could be modulated by signals related to those seen in the ventral striatum.

To allow differentiation of factors related to reward and motivation from factors related to pattern recognition, we combined a behavioral paradigm used previously to study ventral striatal neurons, visually cued reward schedules (Bowman et al. 1996; Shidara et al. 1998), with a behavior paradigm frequently used to study visual pattern recognition, DMS. In the task here, the monkeys were required to complete schedules requiring one, two, or three correct DMS trials to obtain a reward. The reward schedules were randomly interleaved. The schedule in effect and progress through it were signaled by the brightness of a visual cue (a simple bar) located above the more complex stimulus patterns used for the DMS trials.

Neurons in both areas showed responses related to both the patterns used in the DMS trials and the visual cues. Some response properties such as DMS pattern-related stimulus selectivity were similar. However, TE and perirhinal neurons also show strikingly different response properties. The latency distribution of perirhinal responses is centered 66 ms later than the distribution of TE responses. Furthermore when the stimuli, here the visual cues, were associated explicitly with the reward schedule, the cue-related responses were very different across these two areas. Neurons in TE either responded to all cues or did not respond to any of the cues, regardless of the schedule. In contrast in perirhinal cortex, responses related to the cue occurred only at some parts of the schedule, even differentiat-

ing across parts of the schedule where the cue's brightness and the monkey's performance were identical. Thus, neurons in area TE carry signals emphasizing stimulus identity, whereas neurons in perirhinal cortex carry additional strong signals about associative behavioral significance of stimuli related to the progress through a predictable schedule of trials.

METHODS

Subjects, behavioral task, and visual stimuli

Two adult rhesus monkeys (*Macaca mulatta*), weighting 7.5 and 8 kg, respectively, were used in this study. The monkey was seated in a primate chair facing a rear projection screen (90 × 90°) located 57 cm away. A black-and-white random dot background covered the whole screen.

The monkeys had to perform a series of sequential DMS trials. These were grouped into reward schedules of one, two, or three trials. Reward was delivered only after the monkey correctly performed the last trial in a schedule. Each trial in a schedule could be referred to by its state within a schedule (i.e., the current trial position in a schedule divided by the length of the current schedule). The *schedule states* were 1/3, 2/3, 3/3 for a three-trial schedule, 1/2, 2/2 for a two-trial schedule, and 1/1 for a one-trial schedule. The progress through a schedule was indicated by a cue (a simple bar of light). The brightness of the cue varied from white to black in direct proportion to the fractional value of the schedule state (Fig. 1A). Reward trials were signaled by the same black bar, even when they ended schedules of different lengths (1/1, 2/2, and 3/3 = 1). The cued-schedule aspect of the task has been used previously to study the effect of motivation on ventral striatal neuronal activity (Bowman et al. 1996; Shidara et al. 1998).

We imposed no requirement for the monkey to notice or use the cue during the task, and there was no explicit punishment for incorrect trials. However, the schedule state advanced and the cue changed brightness only after a correct trial. After an error, the schedule state did not change, and the same cue reappeared in the next trial. A reward was delivered after successful completion of the final trial of a schedule. A new schedule was picked pseudorandomly after a reward. There was no relationship between the specific DMS pattern appearing on a given trial and progress through the schedule.

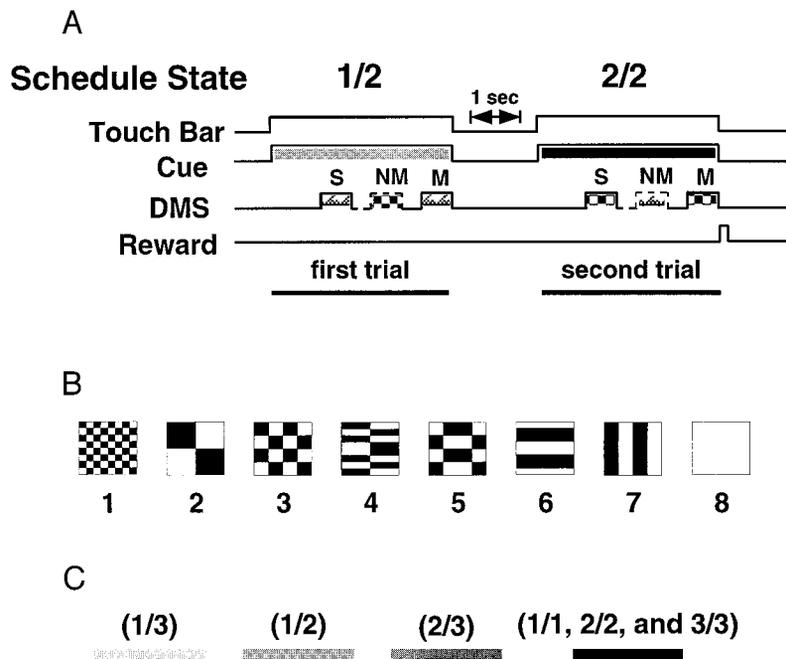


FIG. 1. A: behavioral paradigm. Diagram shows the timing sequence of different events in a 2-trial reward schedule. Numbers on the top of the figure show the schedule states of the trial. Labels on the left of the figure mark the event of the timeline. **Touch Bar**, when a touch-bar is contacted and when it should be released in a correctly performed trial. **Cue**, when the schedule cue is presented and when it is turned off. Long horizontal bars in the time period where the cue is on show the relative brightnesses of the cues used in this 2-trial schedule. Gray bar is the cue for schedule state 1/2, whereas the dark bar is the cue for schedule state 2/2. **DMS** shows the event sequence of sequential delayed match-to-sample (DMS) trials, where S is the sample stimulus, NM is the nonmatching stimulus, and M is the matching stimulus. A random number of nonmatching stimuli (from 0 to 3) are used in a DMS trial (shown by the dashed line). **Reward** shows when a reward is given (upward squarewave, only at the end of the schedule). Long line with label in the bottom of the figure shows the trial number (shown by the dashed line). **B**: stimulus patterns used in the DMS phase of the trial—a set of 8 two-dimensional black-and-white Walsh patterns (Eskandar et al. 1992). **C**: bars with different brightnesses used as visual cues. Schedule states are shown on top of the corresponding cues.

Three sets of visual stimuli were used. 1) A small gray dot ( $0.5^\circ$  in visual angle) was used as fixation spot. This was located directly in front of the monkeys at the center of the screen. 2) Eight two-dimensional ( $8.5 \times 8.5^\circ$ ) black-and-white patterns were used as stimuli presented in the DMS trials (Fig. 1B), referred to as the *DMS patterns* throughout. These also appeared at the center of the screen. When a pattern appeared it obscured the fixation point. 3) Four gray bars ( $4 \times 75^\circ$ ) of varying brightness were used as visual cues (Fig. 1C), referred to as the *cue* throughout. The cue was displayed  $26^\circ$  above the center of the screen.

A two-trial reward schedule is shown in Fig. 1A. For each trial, the monkey started the trial by contacting a touch bar (labeled Touch Bar in Fig. 1A). Immediately after the touch bar was contacted (20 ms), a visual cue was displayed near the top of the projection screen and remained on throughout the trial without changing (labeled Cue in Fig. 1A). A fixation spot appeared in the center of the screen 220 ms after the onset of the visual cue. The monkey was required to fixate loosely (within  $\pm 5^\circ$  of the fixation spot) for the whole trial. Both the cue and fixation spot were displayed for 900–1,000 ms before the trial progressed to the DMS phase. In the DMS phase of the trial (labeled DMS in Fig. 1A), a sample pattern, *S*, replaced the fixation point. Then a random number (0, 1, or 2) of nonmatching patterns, *NM*, appeared in sequence before the original pattern (matching pattern) reappeared, *M*. Sample and nonmatching stimuli were displayed for 500–1,000 ms. The interstimulus interval was 300–800 ms. When the original pattern reappeared, the monkey was required to release the bar within 2 s to indicate a match. A reward was delivered after the monkey performed the last trial in the schedule correctly (labeled Reward in Fig. 1A). A trial was counted as correct if the monkey released the bar within 2 s; otherwise an error was registered. An error also was registered if the monkey moved its eyes beyond the fixation limit. The mean reaction times were  $\leq 500$  ms (see RESULTS).

We also used a version of the same task in which the cue was shuffled randomly with respect to the schedule. In this shuffled task, the cue no longer reflected the schedule state. In the following text, the visually cued task is referred to as the *cued condition*, and the randomly shuffled task is referred to as the *shuffled condition*.

### Training procedures

Monkeys initially were trained to perform DMS with each correct trial being rewarded (a 1-trial schedule). The cue was present, but didn't change. After the monkey learned to perform DMS trials ( $>90\%$  correct), randomization among the three schedules was started abruptly. Within a few minutes, the monkeys' behavior began to show the influence of the cue. The effect of the cue on the monkey's behavior stabilized within 1 wk.

The shuffled condition of the task was introduced when the monkeys' performances of the cued task were stable. In the shuffled condition, the monkeys performed as if the cue was ignored (see RESULTS). The monkeys performed the shuffled task on the day it was introduced. Switching the task between cued and shuffled conditions then was introduced. The cued and shuffled tasks were run in blocks of trials. When the condition was switched, it was switched without warning. After one or two sessions of experience, the monkeys' behavior switched as soon as they discovered that the cue had become meaningful or not, depending on the direction of the switch. Single neuronal recording began after the monkeys were experienced in the switching.

Before the surgical preparation of the monkeys, there was no requirement for the monkeys to fixate. Once the monkeys' behavioral performance stabilized, the monkeys were prepared for electrophysiological recording.

### Surgical preparation

After the monkeys were trained to perform the behavioral task, a cylinder for microelectrode recording and a head holder were affixed

to the skull during an aseptic surgical procedure performed with the animal under isoflurane anesthesia. A scleral magnetic search coil for measuring eye movement was implanted during the same surgery (Judge et al. 1980; Robinson 1963). The monkeys were given a 2-wk postoperative recovery period. The monkeys were retrained to the task with a loose fixation requirement (within  $\pm 5^\circ$  of the fixation spot).

### Single-neuron recording

Single-neuron data and behavioral data were collected while the monkeys performed the cued reward schedules in both the cued and shuffled conditions. A hydraulic microdrive was mounted on the recording cylinder, and tungsten microelectrodes with impedance of 1.5–1.7 M $\Omega$  (Roboz-Microprobe, Rockville, MD) were inserted through a stainless steel guide tube. Experimental control and data collection were performed by a PC, using the REX real-time data-acquisition program (Hays et al. 1982) adapted for the QNX operating system. Single-neuron activities were isolated by first calculating principal components then thresholding their values (Abeles and Goldstein 1977; Gawne and Richmond 1993). Single-neuron activities and all relevant behavioral data were stored with 1-ms time resolution.

All of the experimental procedures described here were in accordance with the *National Institutes of Health Guide for the Care and Use of Laboratory Animals* and were approved by the Animal Care and Use Committee of the National Institute of Mental Health.

### Recording sites localization

We used magnetic resonance imaging (MRI) to confirm the single-neuron recording locations (Saunders et al. 1990). A microelectrode was inserted into the monkey's cortex before MRI as a landmark to indicate the recording locations. The recording areas, on the lateral-medial plane, for both perirhinal cortex and TE of one monkey are shown in Fig. 2. On the anterior-posterior plane, TE recording was carried out in the area from +14 to +17, whereas perirhinal recording was from +18 to +23. Neurons were recorded from comparable areas in a second monkey.

### Data analysis

Behavioral performance was measured using both reaction time and error rate. The reaction times were measured from the onset of the match stimulus to bar release. The behavioral performances were calculated for each schedule state in the cued condition or each cue brightness in the shuffled condition.

The stimulus-related neuronal responses were measured by counting the number of spikes during a 350-ms interval starting 80 ms after

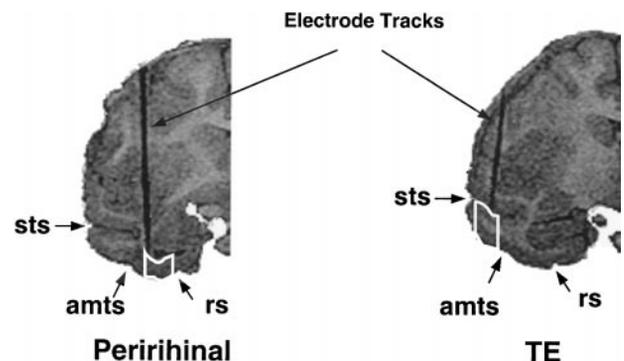


FIG. 2. Recording sites in 1 monkey localized using magnetic resonance images. *Left*: electrode artifact (black line) ending at the most lateral and uppermost border of the actual recording area for perirhinal neurons (outlined in a white box). *Right*: electrode ending at the uppermost border of the actual recording area (outlined in a white box) for TE neurons. Recording areas in the 2nd monkey were comparable with those shown for the 1st monkey.

onset of the stimulus (either a cue or a DMS pattern) for perirhinal neurons and starting 50 ms after stimulus onset for TE neurons. Different starting times for spike counting were used in measuring neuronal responses in TE and perirhinal cortex because perirhinal neurons had longer latencies. Spontaneous activity was measured during 350 ms before the onset of the cue. Statistical significance of the results was evaluated at the 0.05 level.

A cue-related response was defined to be the neuronal response elicited by the cue during the time period when the cue was displayed alone, i.e., the 500 ms immediately after the cue's onset. A DMS pattern-related response was defined to be the neuronal responses elicited by a DMS pattern in the DMS trial.

### Latency measurement

Except for the special case in which there is no ongoing activity preceding stimulus onset, determining the latencies of neuronal responses to that stimulus remains a difficult issue. Overall, probably the best way to estimate latency is by eye. However, we wished to have some objective quantitative estimate. We used a procedure to estimate latency of a response using the average spike density from all of the trials related to one stimulus. We avoided the additional difficulty of estimating trial-by-trial latency.

In the method used here, the average spike density function was formed for the responses related to each stimulus by convolving the responses with a Gaussian having a fixed standard deviation (Richmond et al. 1987). For this average spike density function, we identified the period of the largest monotonic rise (or fall) in the 500 ms after stimulus onset. For each stimulus, we then identify the first point in the monotonic rise that was higher than the highest point of activity during the 200 ms before stimulus onset. The time of this first point was the estimated latency for the response elicited by this stimulus.

Obviously, the standard deviation of the Gaussian used to form the spike density function strongly influences the latency estimation. If the bandwidth is too wide (that is preserving too much high-frequency information), fluctuations due to high-frequency noise will interfere with identifying the overall trend thus interfering with the estimate of the largest monotonic rise. The onset of stimulus-related responses should occur at a more consistent time than any background fluctuation, rising or falling at about the same time across trials. Thus the

response onset should be observable across a wide range of bandwidths. Therefore average spike density functions were formed using Gaussians having standard deviations ranging from 5 to 45 ms in 5 ms steps. For each Gaussian standard deviation, we formed a vector of latency estimates from all of the stimulus conditions being considered e.g., for all of the DMS pattern-related responses. These vectors then were correlated with the vectors obtained from the next larger Gaussian standard deviation. Typically as the Gaussian becomes wider (the bandwidth becomes lower) the correlation rises and eventually reaches an asymptotic value (Fig. 3). Our final estimates of the latencies are taken from the data filtered with the narrowest Gaussian reaching the asymptotic correlation value. To account for noncausality of the Gaussian, we added half the standard deviation of the final Gaussian to each latency value, making it possible to compare values from different Gaussians. The Gaussian standard deviations were typically 20–30 ms.

This procedure works well for these data, giving values that are consistent with values we would have chosen by eye (see Fig. 7). The same procedure can be and was applied to periods of inhibition.

## RESULTS

Behavioral and electrophysiological data were obtained while the two adult rhesus monkeys (*M. mulatta*) performed randomly interleaved reward schedules of one, two, or three DMS trials in both the cued and shuffled conditions.

### Behavior

Although the monkeys were free to ignore the cue indicating the schedule progress, their behavior was influenced consistently by it. In the cued condition, both the mean reaction times and the mean error rates were strongly related to the schedule states (Fig. 4). As the end of a schedule approached (indicated by the brightness of the cue), the monkeys released the touch bar more quickly and made fewer errors. The monkeys showed the shortest reaction times and fewest errors when the cue (a dark bar) indicated that a reward would be delivered if the current trial was completed successfully. For both monkeys,

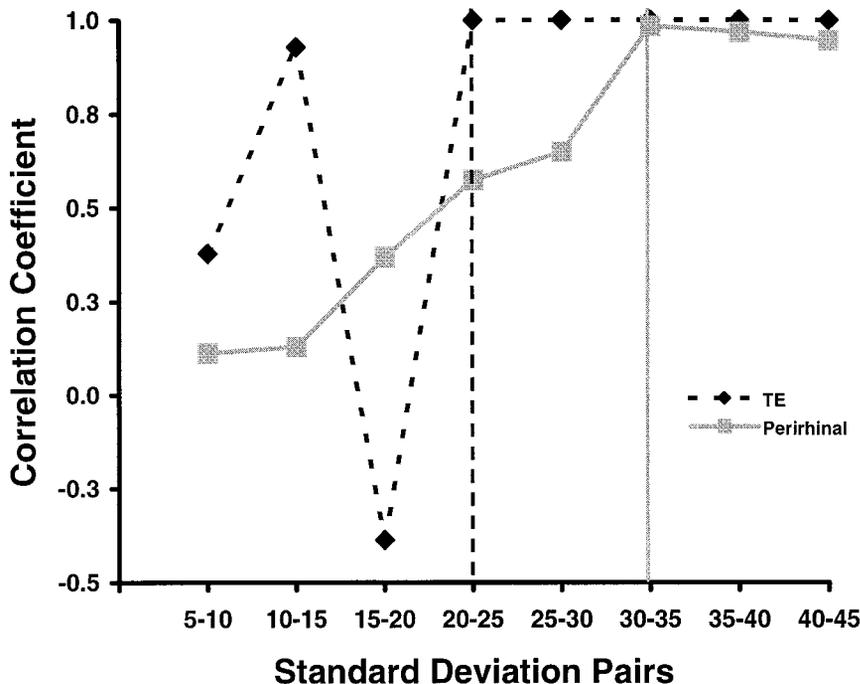


FIG. 3. Correlation coefficients of estimated latencies using different Gaussian bandwidths (see text). For TE neuron (*ip03r01*), the narrowest Gaussian reaching the asymptotic correlation value is 20 ms (the dotted vertical line), whereas for perirhinal neuron (*p2p03r01*), the narrowest Gaussian is 30 ms (the solid vertical line).

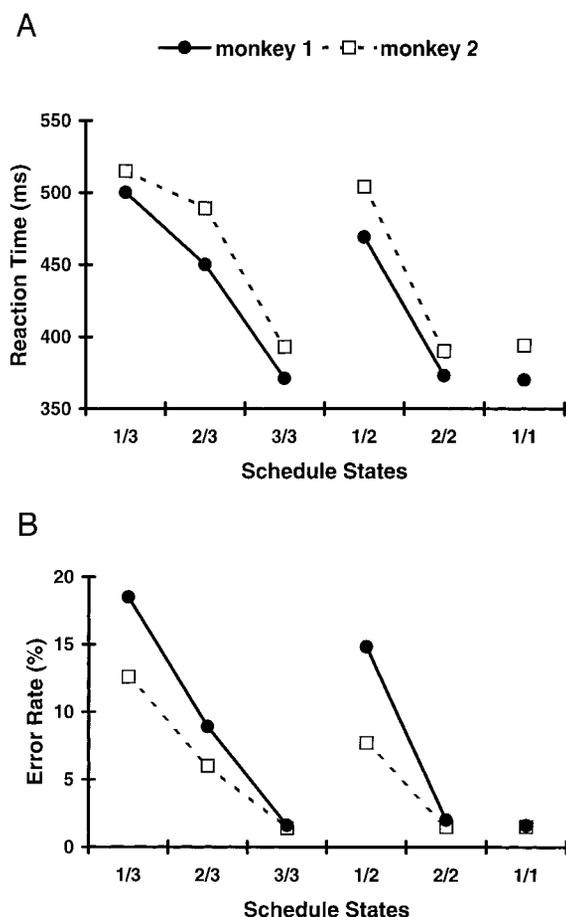


FIG. 4. Behavioral performance in the cued condition. Abscissa shows the schedule states. Ordinate shows the mean reaction times in the correct trials (A), and the proportion of error trials in all trials (B). Each point is made up from data collected from 1 monkey across the entire set of single-unit recording sessions. Both monkeys make fewer errors and react more quickly as the schedule state gets closer to the reward.

the mean reaction times and mean error rates were the same on the final trial (i.e., the rewarded trial) of all three schedules (1, 2, or 3; single-factor ANOVA, NS). Thus for behavioral analysis, we can treat all of the final trials of all schedules as if they are the same. When that is done, there is a strong linear relation between the brightness of the cue and both the mean reaction time [linear regression,  $F(1,2) = 35.45$ ,  $P < 0.05$ , Fig. 5A] and mean error rate [ $F(1,2) = 385.70$ ,  $P < 0.05$ , Fig. 5B]. In addition, almost all of the variance in either the mean reaction times or mean error rates can be explained by the cue's brightness (linear regression, reaction time:  $R^2 = 0.95$ ; error rate:  $R^2 = 0.99$ ). When the cues were shuffled randomly so that the brightness of the cue no longer indicated the schedule state of the current trial (the shuffled condition), the cue's brightness no longer affected the monkeys' behavior [single factor ANOVA, mean reaction time:  $F(1,2) = 0.92$ , NS; mean error rate:  $F(1,2) = 4.28$ , NS; Fig. 5].

This result shows that the monkeys treated the shuffled condition of this task as a task with a variable-ratio reward schedule (Mackintosh 1983). In past reports, when monkeys were asked to perform a similar behavioral task in which each trial was a color discrimination (Shidara et al. 1997), the monkeys were maximally motivated in the shuffled condition. Here, however, the mean reaction times of the final trials in the

cued condition were faster than the mean reaction times of all trials in the shuffled condition (Wilcoxon rank sum test,  $W = 30$ ,  $P < 0.05$ ; 1-tailed test), and the mean error rates of the final trials in the cued condition were smaller than the mean error rates of all trials in the shuffled condition (Wilcoxon rank sum test,  $W = 22$ ,  $P < 0.05$ ; 1-tailed test). So the monkeys' behavior in the shuffled condition was poorer than that of the maximally motivated states (the final trials) in the cued condition. Thus it appears that the monkeys were less than maximally motivated on a trial-by-trial basis in the shuffled condition.

#### Electrophysiology

Single neurons were recorded from both hemispheres of one monkey and one hemisphere of the other monkey. All of the stimuli, both cues and DMS patterns, elicited neuronal responses from some neurons of both TE and perirhinal cortex. Responses related to cue appearance are referred to below as *cue-related responses*. Responses related to DMS pattern appearances within the DMS trial are referred to in the following text as *DMS pattern-related responses*. Inspection showed that the neuronal responses were phasic. In every case, phasic cue-related responses ended well before the sample pattern in a DMS trial appeared, so there were no overlaps between cue-related responses (from the period when the cue is displayed alone) and DMS sample pattern-related responses (from the period when the sample pattern is displayed).

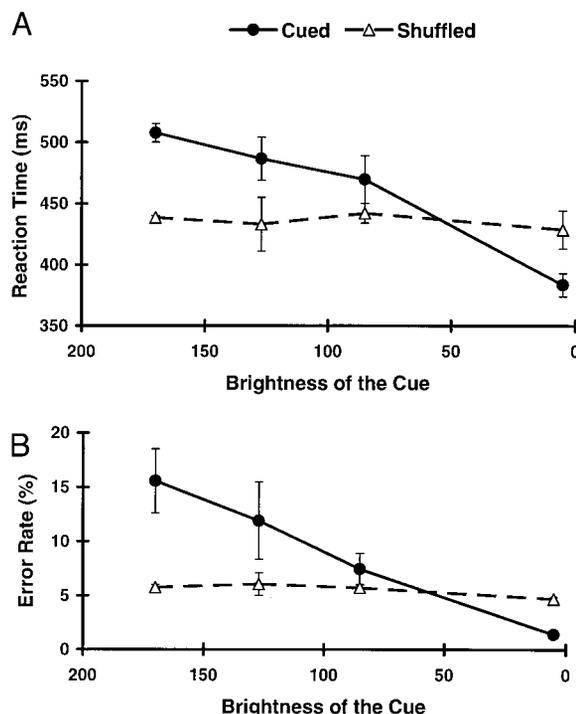


FIG. 5. Relationship between monkeys' behavioral performance and the cue's brightness in both the cued condition and shuffled condition. Abscissa shows the cue's brightness on an arbitrary scale from 0 to 200 (corresponding to brightness of the computerized brightness scale). The smaller the number, the darker the cue. Ordinate shows the mean reaction times in the correct trials (A), and the proportion of error trials in all trials (B). Each point represents data averaged over 2 monkeys across all single-neuron recording sessions (bars indicating SEs). ●, data from the cued condition; △, data from shuffled condition.

We recorded from 107 TE neurons (73 from *monkey 1* and 34 from *monkey 2*) and 97 perirhinal neurons (45 from *monkey 1* and 52 from *monkey 2*). In all of the analyses related to latency and response strength, the data from the two monkeys were combined because there were no statistically significant differences between them. Among the TE neurons, 3 (3%) had responses related to the cue only, 16 (15%) had responses related to both the cue and DMS patterns, and 34 (32%) had responses related to one or more DMS patterns but not to the cue. The remaining 54 TE neurons did not show stimulus-related responses. Among the perirhinal neurons, 11 (11%) had responses related to the cue only, 22 (23%) had responses related to both the cue and one or more DMS patterns, and 8 (8%) had responses related to one or more DMS patterns but not to the cue. The remaining 56 perirhinal neurons showed no

stimulus-related responses. None of the perirhinal neurons or TE neurons studied showed responses related to bar release or reward, as has been seen in ventral striatum (Bowman et al. 1996; Schultz et al. 1992; Shidara et al. 1998).

To examine the latencies in area TE and perirhinal cortex, we measured the latency for every response that was significantly larger than the background (see METHODS). There was a surprisingly large difference in the latency distributions between TE and perirhinal neurons (Kruskal-Wallis test,  $P < 0.05$ ; Fig. 6A) with the median being 66 ms longer in perirhinal cortex (TE: median 78 ms, interquartile range 60–115 ms,  $n = 282$ ; perirhinal: median 144 ms, interquartile range 109–185 ms,  $n = 233$ ). In contrast, the firing rate distributions overlapped almost completely (TE: median 14 spikes/s, interquartile range 10–20 spikes/s,  $n = 282$ ; perirhinal: median 11

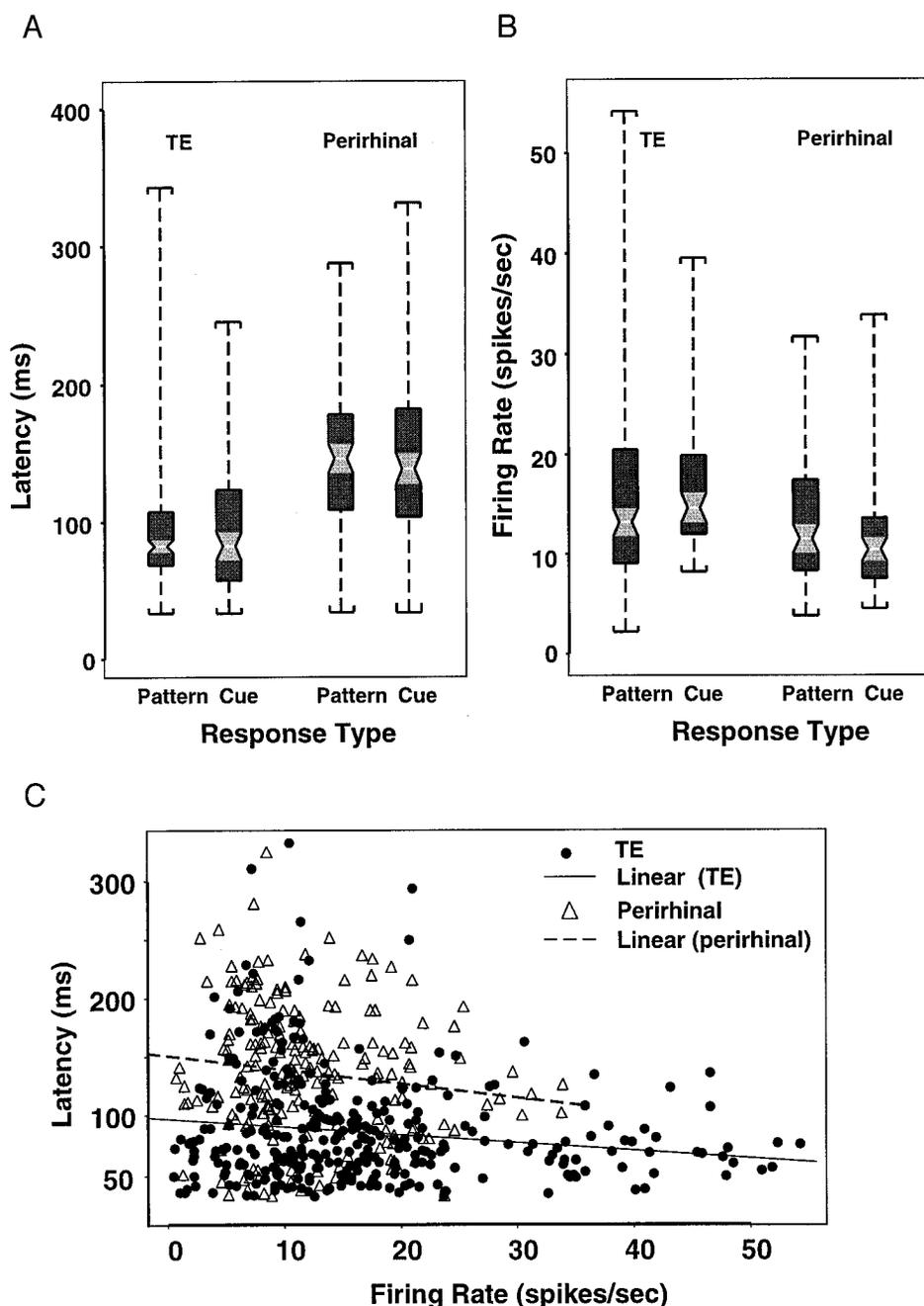


FIG. 6. Distribution of latency and firing rate (A and B) and the relationship between latency and firing rate (C). Abscissa shows the response types in A and B. Ordinates show the response onset latency (A) and the firing rate (B). For each data bar plotted in the figure, the white line in the middle is the median value of the data; the light gray area shows the 95% confidence interval for the median, the dark gray area shows the interquartile range of the data, and the whiskers are drawn to cover the full data range. A: latency distributions of responses related to either DMS patterns or cues for TE neurons and perirhinal neurons, respectively. There is no difference in latency distribution between DMS pattern-related responses and cue-related responses in either TE neurons or perirhinal neurons. However, the median latency is 66 ms longer in perirhinal cortex. B: firing rate distributions of responses related to either DMS patterns or cues for TE neurons and perirhinal neurons, respectively. Firing rate distributions overlap considerably between responses of TE neurons and perirhinal neurons. C: abscissa shows the firing rate and the ordinate shows the latency. Linear (TE) and Linear (perirhinal) show the linear regression lines for TE and perirhinal neuronal responses, respectively. Intercepts are statistically different whereas the slopes of the regression lines are statistically indistinguishable (see text).

spikes/s, interquartile range 8–15 spikes/s,  $n = 233$ ; Fig. 6B). There was no difference in distribution of either latency or firing rate between the cue-related responses and pattern-related responses in either TE or perirhinal cortex (Kruskal-Wallis test, NS). The background activity in these two areas (taken from the 350-ms period before the cue appeared when there was a significant response anywhere in the trial) was similar (TE: median 7.8 spikes/s, interquartile range 5.3–11.5 spikes/s,  $n = 53$ ; Perirhinal: median 8.6 spikes/s, interquartile range 4.9–11.6 spikes/s,  $n = 41$ ; Kruskal-Wallis test, NS).

The strengths of stimulus-elicited responses for perirhinal neurons were significantly lower than those for TE neurons (Kruskal-Wallis test,  $P < 0.05$ ). Latency covaries with response strength to a small degree in both areas (Linear regression,  $P < 0.05$ ; perirhinal: slope =  $-1.20$ , intercept =  $150$ ; TE: slope =  $-0.65$ , intercept =  $95$ ; Fig. 6C). The intercepts of these linear regressions were significantly different ( $t$ -test,  $t$ -value =  $9.5$ ,  $P < 0.05$ ), and the slopes were statistically indistinguishable ( $t$ -value =  $0.63$ , NS). Thus the difference in latency was consistent across the range of overlapping response strengths.

**DMS PATTERN-RELATED RESPONSES AND INFLUENCE OF DMS PHASE ON THESE RESPONSES.** Fifty TE neurons and 30 perirhinal neurons responded to DMS patterns displayed in the DMS phase of the trial. The neurons responding to the DMS patterns displayed as sample stimuli, referred to as *sample responses*, always responded to the same patterns when they were displayed as nonmatch or match stimuli.

Of the 50 TE neurons responding to the DMS patterns, 46 showed stimulus selectivity in sample responses (single factor ANOVA,  $R^2 = 0.20 \pm 0.03$ , mean  $\pm$  SE,  $n = 46$ ,  $P < 0.05$ ; Fig. 7). The percentage of TE neurons showing stimulus selectivity is similar to that seen previously (Desimone et al. 1984; Gross et al. 1972; Tanaka et al. 1991). Of the 30

perirhinal neurons with responses related to DMS patterns, 27 showed stimulus selectivity in the sample responses (single-factor ANOVA,  $R^2 = 0.10 \pm 0.02$ ,  $n = 27$ ,  $P < 0.05$ ; Fig. 7). The percentage of perirhinal neurons showing stimulus selectivity is also similar to that reported previously (Nakamura et al. 1994; Riches et al. 1991).

We examined whether the DMS pattern-related responses were influenced by the behavioral context of DMS (i.e., sample, nonmatch, and match in which the stimulus was displayed). The number of nonmatching stimuli appearing in a trial varied from 0 to 3. Only the responses from the first nonmatching stimuli were used for this analysis even if more than one nonmatching stimulus appeared in the DMS. Also, sample and match responses were taken only from the trials with at least one nonmatching stimulus to ensure equal numbers of trials in sample, match, and nonmatch responses.

As reported previously (Eskandar et al. 1992), although the average firing rates of both the nonmatch and match responses were slightly stronger than the sample responses averaged over the 50 TE neurons, there was no statistically significant difference among them [single-factor ANOVA,  $F(2, 575) = 0.78$ , NS]. Similarly, there was no difference in the mean spike firing rates averaged over all 30 perirhinal neurons in the sample, nonmatch, and match conditions [single-factor ANOVA,  $F(2, 283) = 0.25$ , NS]. However, previous studies have shown that the behavioral context of DMS could significantly affect the pattern-related responses of individual neurons (Eskandar et al. 1992; Miller et al. 1991a). Therefore we examined the effect of behavioral context of DMS across all patterns for each neuron using ANOVA.

DMS pattern-related responses of one TE neuron showing a significant influence of DMS phase are shown in Fig. 8. This neuron responded to all eight stimuli displayed in all three DMS phases. All responses were excitatory except those elic-

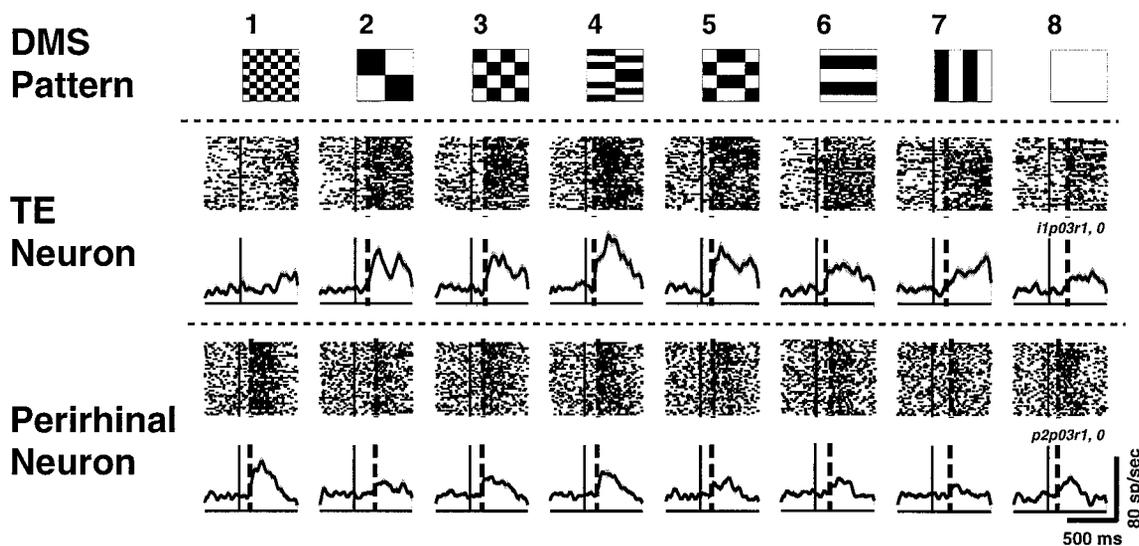


FIG. 7. DMS pattern-related neuronal responses of a TE neuron and a perirhinal neuron. Neuronal responses are shown in both the spike raster dots diagrams (*top*) and spike density function plots (*bottom*). Abscissa in both the rasters and spike density plots represents time. In a raster, the ordinate represents the neuronal responses to the same experimental condition over time (earliest trial at the *top*), and each dot represents the time of an emitted spike. In a spike density plot, the ordinate shows instantaneous firing frequency averaged over all trials at a 1-ms resolution. Black curve, mean; gray areas on both sides of the curve, SEs at each point in time. Solid vertical lines in the raster and spike density plots: stimulus onset. Responses are aligned to stimulus onset and are shown from 300 ms before to 550 ms after stimulus onset. Time scale and firing rate scale are shown at the *bottom right*. Dashed line in each plot indicates the estimated latency of that response. Both the TE and perirhinal neurons show strong stimulus selectivity. Time scale at the *bottom right* represents 500 ms, and the response scale at the *bottom right* represents 80 spikes/s.

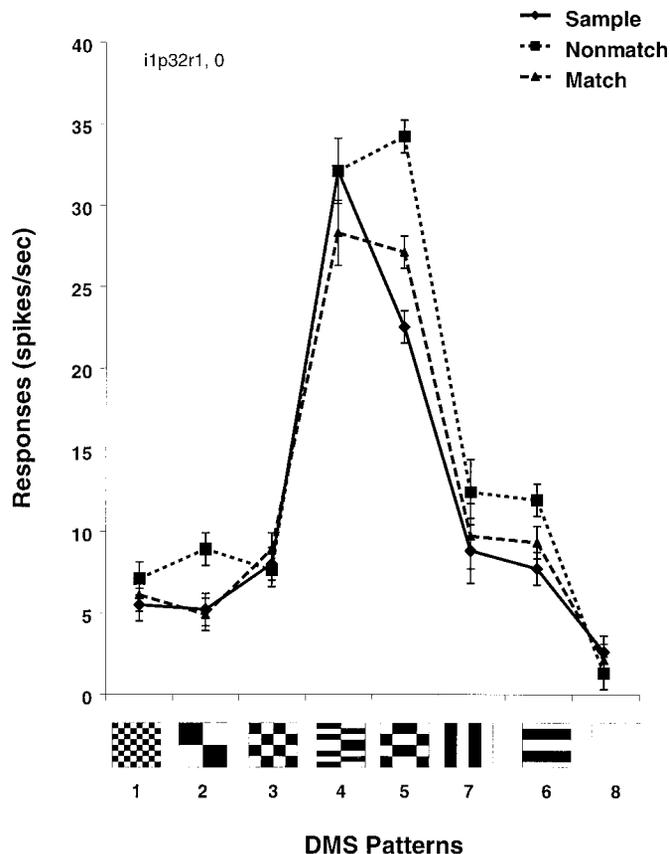


FIG. 8. DMS pattern selectivity of a TE neuron in different phases of a DMS trial showing that behavioral context significantly affected DMS pattern-related responses. —, sample responses. ···, nonmatch responses; ---, match responses. Bars show SEs. Stimuli are numbered as in Fig. 1. Neuron showed stimulus selectivity in all 3 phases of a DMS trial, i.e., sample, nonmatch, and match. However, the behavioral context of DMS also affected this neuron's responses significantly (2-way ANOVA,  $P < 0.05$ ; see text).

ited by a white square (numbered 8), which were inhibitory. This neuron showed stimulus selectivity in all three DMS conditions. The effect of the behavioral context was significant [behavioral context term of the 2-way ANOVA,  $F(2,1533) = 9.67$ ,  $P < 0.05$ ], but small ( $R^2 = 0.006$ ). There was also a significant nonlinear interaction between the DMS patterns and behavioral context of DMS [interaction term of the 2-way ANOVA,  $F(14, 1533) = 2.77$ ,  $R^2 = 0.01$ ,  $P < 0.05$ ]. Thus for this neuron DMS phase accounted for 1.6% of its response variance.

We carried out this same analysis for all 50 TE neurons that responded to the DMS pattern. Twenty-one (42%) showed significant interactions between DMS pattern and behavioral context of DMS (interaction term of the 2-way ANOVA,  $P < 0.05$ ). For these 21 neurons, the average variance accounted for by the behavioral context was  $0.02 \pm 0.01$  ( $n = 21$ ). Of the 30 perirhinal neurons that responded to the DMS pattern, 8 (26%) showed significant interactions between DMS pattern and behavioral context of DMS (interaction term of the 2-way ANOVA,  $P < 0.05$ ). Again, the proportion of average variance accounted for by the context was  $0.02 \pm 0.01$  ( $n = 8$ ).

Thus as has been reported before (Eskandar et al. 1992), there was a small (~2% of response variance), but significant, effect of behavioral context in DMS task for a substantial

proportion of TE neurons. A small percentage of the perirhinal neurons showed the same small effect.

INFLUENCE OF SCHEDULE STATES ON THE DMS PATTERN RESPONSES. To determine whether the schedule states influence the neurons' responses to the DMS patterns, we combined the responses to a given pattern from the sample period with the responses induced by the same pattern from the match period for the neurons that showed no significantly different

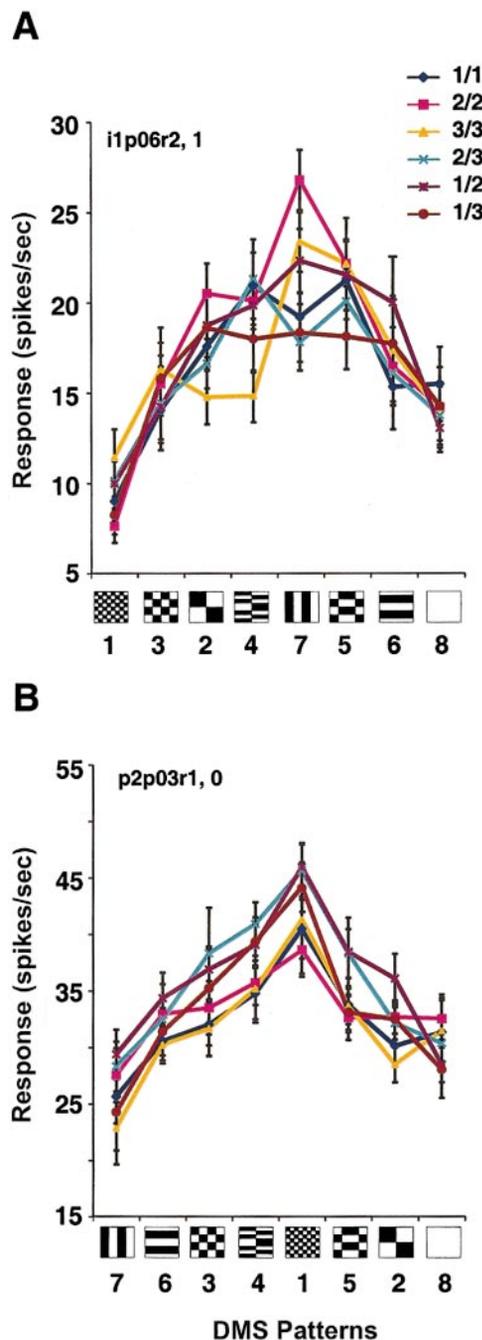


FIG. 9. DMS pattern selectivity of a TE neuron (A) and a perirhinal neuron (B) in different schedule states, respectively. Each color curve represents the response in 1 schedule state. Bars show SEs. Stimuli are numbered as in Fig. 1. A: this TE neuron showed stimulus selectivity in all 6 schedule states as well as an effect of schedule states (2-way ANOVA,  $P < 0.05$ ; see text). B: this perirhinal neuron showed similar stimulus selectivity in all 6 schedule states, but no effect of schedule state, per se (2-way ANOVA, NS; see text).

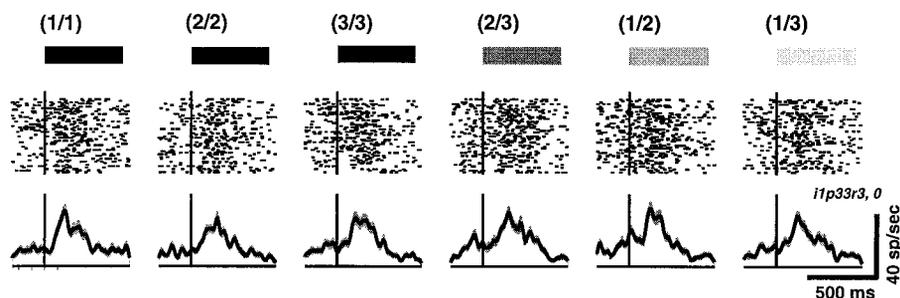


FIG. 10. Cue-related responses of a TE neuron. Conventions as in Fig. 7. Although this neuron shows a small degree of response modulation related to the cue's brightness, the cue elicits strong responses in all schedule states. Thus the responses of this TE neuron signal that the cue has appeared regardless of the schedule states (see text). Time scale at the bottom right represents 500 ms, and the response scale at the bottom right represents 40 spikes/s.

responses in the two periods. If there was a difference between sample and match responses, then only the sample responses were used in the analysis. In addition, only neurons with at least five trials in each schedule state of any given stimulus were used in the analysis.

Neuronal responses from 23 TE neurons were analyzed; for 15 neurons, the responses from the sample and match periods were combined, and for the other 8, the responses from sample period only were used. Neuronal responses from 19 perirhinal neurons were analyzed; for 11 neurons, the responses from the sample and match periods were combined, and for the other 8, the responses from the sample period were used.

The schedule states had a significant influence on the DMS pattern-related responses in 4 of 23 (17%) TE neurons. The TE neuron shown in Fig. 9A responded selectively to the DMS patterns in all schedule states. However, the schedule states influenced both the firing rate and selectivity of the neuron [interaction term of the 2-way ANOVA,  $F(35, 1490) = 2.53$ ,  $R^2 = 0.05$ ,  $P < 0.05$ ]. The averaged variance accounted for by the schedule states on the DMS pattern-related responses for the 4 TE neurons was  $0.04 \pm 0.01$  ( $n = 4$ ). For the remaining 19 TE neurons, the schedule had no influence on the DMS pattern-related responses (interaction term of the 2-way ANOVA, NS).

The schedule states did not influence the DMS pattern-related responses of any of the 19 perirhinal neurons (interaction term of the 2-way ANOVA, NS). A perirhinal neuron's responses to the DMS patterns in all six schedule states are shown in Fig. 9B. Although the neuron responded selectively to the DMS patterns, the schedule states as a set had no effect on the responses [interaction term of the 2-way ANOVA,  $F(35, 892) = 0.72$ , NS]. Nor did any pair of states yield a significant difference. Thus in our sample the schedule states had a small effect on the DMS-pattern elicited responses of a few TE neurons but not on those of any perirhinal neuron.

**CUE-RELATED RESPONSES.** For all 19 TE neurons showing cue-related responses the responses occurred in all schedule states (example in Fig. 10). Five of the TE neurons responded identically to the cue's appearance regardless of the schedule state or the cue's brightness (single-factor ANOVA, NS). The 14 remaining TE neurons showed response modulation across cues. The same amount of the response variance ( $R^2 = 0.05 \pm 0.01$ ;  $n = 14$ ) could be explained by the four cue brightnesses as by the six schedule states (paired  $t$ -test, NS; Fig. 11). Furthermore, for all of those 14 TE neurons, the responses in the reward states (i.e., 1/1, 2/2, and 3/3 states in which the cues are the same dark bar) were indistinguishable (single-factor ANOVA, NS). Thus the modulation of cue-related responses exhibited by TE neurons appears to be related to the brightness

of the cue, suggesting, in line with previous interpretations, that TE neurons respond to stimulus identity (Tanaka 1996).

The responses of perirhinal neurons to the cue were qualitatively different from those of TE neurons in that the variance in the cue-related responses was better explained when it was related to the six schedule states than to the four brightnesses. All of the 33 perirhinal neurons with cue-related responses showed schedule-related selectivity (single-factor ANOVA,  $P < 0.05$ ). Of those, 30 responded in one or more reward states. The 22 that responded in only one or two of the three reward states were expected to and did show significant selectivity for particular reward states. Of the eight remaining neurons responding in all three reward states, four showed significant response selectivity across the reward states (single-factor ANOVA,  $P < 0.05$ ).

The response selectivity is often manifested by ON-OFF gating related to the schedule (example in Fig. 12). Twenty-five of the

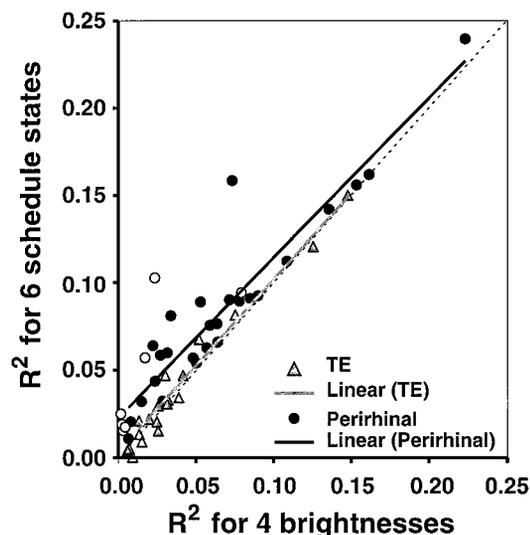


FIG. 11. Variance in cue-related responses accounted for ( $R^2$  in single factor ANOVA) by either the 4 brightnesses of the cues or the 6 schedule states associated with the cues.  $\cdots$ , equality line. Linear regression line [Linear (Perirhinal)] for the perirhinal neurons is significantly above the equality line, whereas the linear regression line [Linear (TE)] for the TE neurons is not. For the 14 TE neurons ( $\blacktriangle$ ) showing significant selectivity (single-factor ANOVA,  $P < 0.05$ ) for both the schedule states and the cue's brightnesses, both the 6 schedule states and the 4 brightnesses of the cue explained the same amount of variance ( $R^2 = 0.05 \pm 0.01$ , mean  $\pm$  SE,  $n = 14$ ; paired  $t$ -test, NS). For the 26 perirhinal neurons ( $\bullet$ ) showing significant selectivity (single-factor ANOVA,  $P < 0.05$ ) for both the schedule states and the cue's brightnesses, the proportion of variance explained by the 4 cue brightnesses ( $R^2 = 0.08 \pm 0.01$ ,  $n = 26$ ) is significantly less (a paired  $t$ -test,  $P < 0.05$ ) than the amount explained by the 6 schedule states ( $R^2 = 0.10 \pm 0.01$ ,  $n = 26$ ).  $\triangle$ , 5 TE neurons that fail to show selectivity;  $\circ$ , 7 perirhinal neurons that are selective for 6 schedule states but not for the 4 brightnesses.

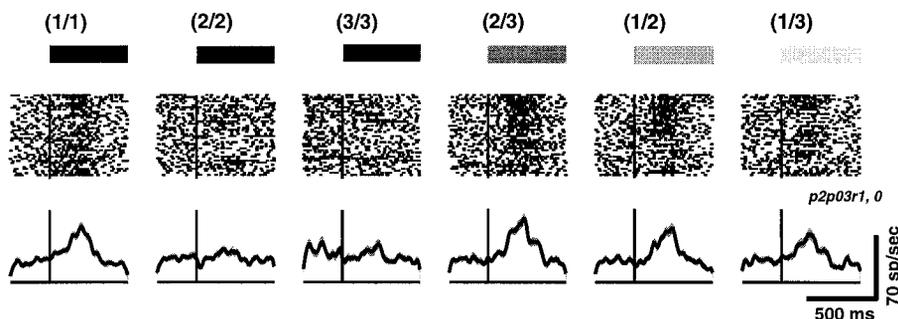


FIG. 12. Cue-related responses of a perirhinal neuron. Conventions as in Fig. 7. This perirhinal neuron shows ON-OFF gating to the visual cue, responding strongly to the cue's appearance in the 1/1, 2/3, 1/2, and 1/3 schedule states but not in the 2/2 and 3/3 states. This neuron's cue-related responses can be interpreted as signaling the beginning or continuation of a reward schedules (see text). Time scale at the *bottom right* represents 500 ms, and the response scale at the *bottom right* represents 70 spikes/s.

perirhinal neurons showed excitatory responses to the cue (example in Fig. 12); the remaining eight showed inhibition (example in Fig. 13).

The neuron shown in Fig. 12 responded strongly only when the cue appeared in the 1/1, 2/3, 1/2, and 1/3 schedule states (paired *t*-test,  $P < 0.05$ ). It did not respond when the cue appeared in the 2/2 or 3/3 schedule states. Thus the cue selectivity exhibited by this neuron appears to be related to the schedule states. Because the neuron was active in the 1/1 schedule state, but not in the 2/2 and 3/3 schedule states which also signaled reward trials, the cue's relation to reward cannot account directly for this neuron's response selectivity. The response profile cannot be explained by the cue's brightness, either. The same cue (a dark bar) was used in the 1/1, 2/2, and 3/3 schedule states, yet the neuron responded only in 1/1 state. Finally, the monkey performed all trials ending in reward equally accurately and quickly regardless of which schedule was in effect (cf. Fig. 4), so it seems likely that the monkey was equally attentive in all three schedule states, 1/1, 2/2, and 3/3. Thus differences in the monkey's attentional effort seem unlikely to account for the response differences. This particular neuron's response could be interpreted either as signaling the beginning (1/3, 1/2, and 1/1) or the continuation (2/3) of a schedule.

Similarly, the neuron shown in Fig. 13 showed strong inhibitions to the cues in 1/1, 1/2, and 1/3 schedule states and showed weak inhibition to the cues in the 2/3 and 2/2 states. It did not respond to the cue in the 3/3 state. The responses of this neuron could be interpreted as signaling the first and second trials of a schedule.

If we regard the cue-related responses of perirhinal neurons as binary, i.e., response versus no response, we can classify all 33 neurons (Table 1). Some neurons ( $n = 7$ ) responded at the beginning of one or more schedules (1/3, 1/2, and/or 1/1; Fig. 14A). Other neurons ( $n = 8$ ) responded at end of one or more schedules (3/3, 2/2, and/or 1/1; Fig. 14B). The remaining neurons ( $n = 18$ ) had selectivities for more complicated com-

binations of schedule states (examples illustrated in Figs. 12 and 13).

The response profiles of all the perirhinal neurons with cue-related responses can be explained by the cue's relation to the schedule. For the perirhinal neurons showing cue-related responses selective for different final trials ending the one-, two-, and three-trial reward schedules, i.e., 1/1, 2/2, and 3/3 states (19 neurons; classes 3, 5, 6, 7, 10, 11, and 12), the cue's relation to the schedule state seems to be the only possible explanation for the response profiles. For remaining perirhinal neurons (14 neurons; classes 1, 2, 4, 8, and 9), the brightness of the cue provides a possible alternative explanation for the response selectivity, whereas for six neurons, the cue's direct relation to reward provides an alternative explanation (classes 4 and 9).

To test further whether the cue's relation to the schedule state was the factor that modulated a perirhinal neuron's cue-related response, 14 cue-responding neurons were recorded in both the cued and shuffled conditions. For 12/14 (86%) neurons the cue-related responses lost their response selectivity during the shuffled condition. Ten neurons stopped responding to any of the cues in the shuffled block (Fig. 15). Two other neurons became responsive to all cues in the shuffled block of the test after showing strong selectivity in the cued condition (Fig. 16).

The last 2 (2/14) neurons maintained the same response profile in the shuffled condition as in the cued condition (2-way ANOVA, NS). Of the two neurons, one responded under both conditions to the appearance of the 1/3 cue (class 1) and the other, to the appearance of 1/3, 2/3, and 1/2 cues (class 4). Thus the interpretation of the responses in the cued condition of these two neurons is ambiguous because they could be selective to the cue's brightness rather than to the schedule state.

The results from an ANOVA support the conclusion that cue-related responses of perirhinal neurons are better explained in terms of schedule states. Fewer perirhinal neurons (26 neurons) showed selectivity for brightness than for schedule

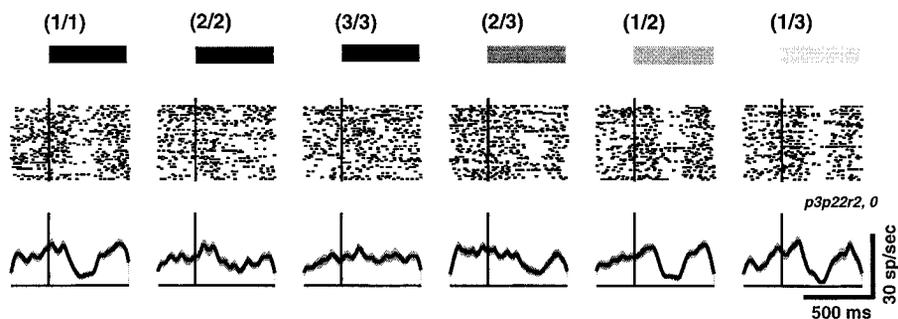


FIG. 13. Cue-related inhibitory responses of a perirhinal neuron. Conventions as in Fig. 7. This neuron shows strong inhibitory responses to the cue's appearance in the 1/1, 1/2, and 1/3 schedule states and weak inhibitory responses to 2/3 and 2/2 states. It does not respond to the cue's appearance in the 3/3 state. This neuron's cue-related responses can be interpreted as signaling the 1st trial and 2nd trial of any schedule, or conversely, it can be signaling the 3rd trial in the 3-trial schedule. Time scale at the *bottom right* represents 500 ms, and the response scale at the *bottom right* represents 30 spikes/s.

TABLE 1. Categories of response profiles of perirhinal neuronal responses related to the cues

Relation to Schedule	Class	Schedule States						No. of Cells
		1/1	2/2	3/3	2/3	1/2	1/3	
Beginning	(1)					✓	✓	1
	(2)					✓	✓	2
	(3)	✓					✓	4
Others	(4)				✓	✓	✓	3
	(5)	✓			✓	✓	✓	5
	(6)				✓	✓	✓	1
	(7)	✓	✓		✓	✓	✓	4
	(8)	✓	✓	✓		✓	✓	5
End	(9)	✓	✓	✓				3
	(10)	✓	✓	✓				1
	(11)	✓	✓					3
	(12)	✓	✓					1

A check mark (✓) indicates a significant response.

state (33 neurons). Furthermore, for all of these 26 perirhinal neurons, the amount of variance explained is greater when six schedule states were used in the ANOVA than when four brightnesses were used (paired *t*-test,  $P < 0.05$ ; Fig. 11).

DISCUSSION

In this study, we identified differences in neuronal response properties between TE and perirhinal neurons. We recorded single neurons from both areas while two monkeys performed delayed match-to-sample trials combined with visually cued reward schedules. The visual cue modulated the monkeys' behavior even though there was no requirement for monkeys to notice the cue. This result led us to believe that monkeys voluntarily adjusted their motivation levels according to the schedule. As expected, there are some similarities in the neuronal response properties of TE and perirhinal cortex. Neurons in both areas show similar response properties when the stimuli are only related to the stimulus recognition such as the DMS patterns. Neurons in both areas show stimulus selectivity to the DMS patterns, and the neuronal responses related to the DMS patterns show a small amount of modulation related to the

behavioral context of the DMS trial. However, we also have shown here that there are large differences in the neuronal response properties of these two areas, particularly when the visual stimuli, here visual cues, are explicitly related to the reward schedule. First, the response latency distribution in perirhinal cortex is far later than would be expected given the large direct projection from area TE. Second, the responses of the perirhinal neurons related to the reward schedule cue seem to be interpreted most parsimoniously as carrying associative information about the reward schedule; in contrast, the cue-related responses of the TE neurons show modulation related to the visual cue that are best interpreted as conveying information about the cue's brightness. Perirhinal cortex may be important for establishing the relation between expected schedules of work and reward.

Motivation

We have used the monkey's behavioral performance to evaluate its motivational level, and it seems likely that the latter is influenced by both aspects of the task: schedule and individual trial. The influence of the schedule on motivation

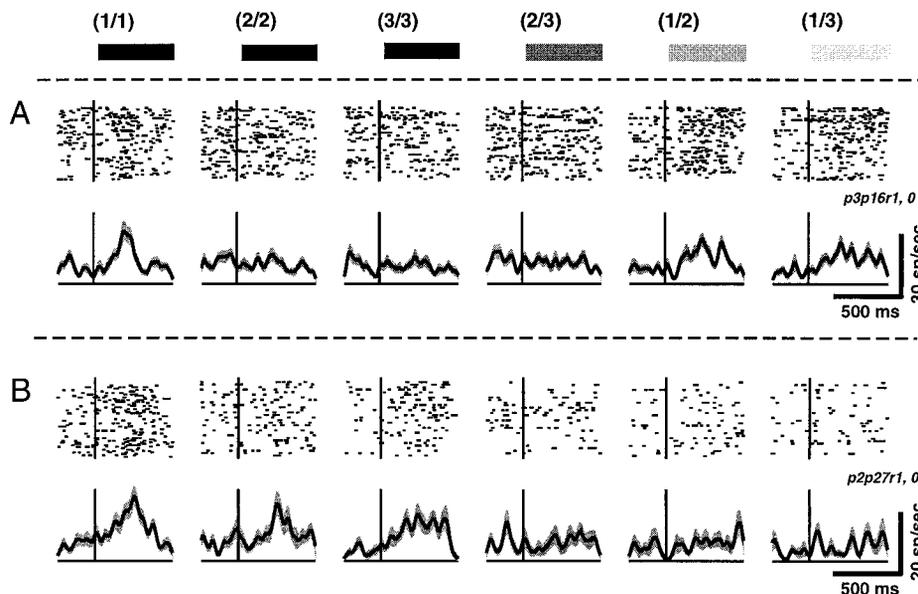


FIG. 14. Cue-related responses of 2 perirhinal neurons. Conventions as in Fig. 7. A: this perirhinal neuron responds to the cue's appearance in the 1/1, 1/2, and 1/3 schedule states but does not respond in 2/3, 2/2, and 3/3 states. Response profile could be interpreted as one signaling the beginning of a schedule. B: this perirhinal neuron responds only to the cue's appearance in the 1/1, 2/2, and 3/3 states but does not respond in the other states and so seems to signal the ending of a schedule. Time scale at the bottom right represents 500 ms, and the response scale at the bottom right represents 20 spikes/s.

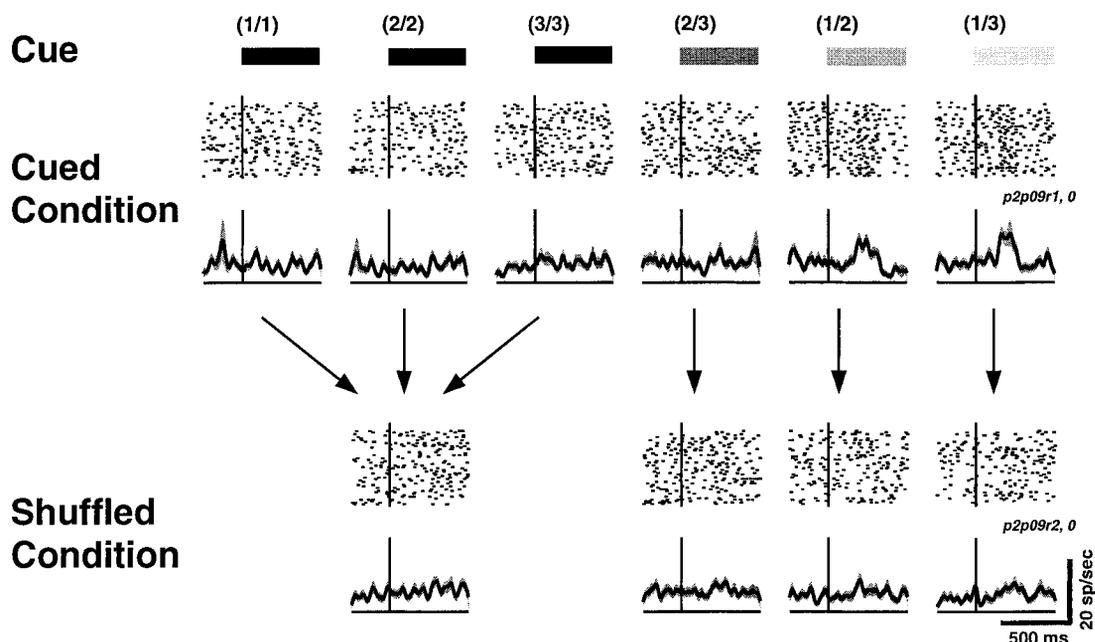


FIG. 15. Cue-related responses of a perirhinal neuron in both the cued and shuffled conditions. Conventions as in Fig. 7. In the cued condition, this neuron responds strongly to the cue's appearance in the 1/3 state and weakly, but significantly, in the 1/2 state. There are no responses to other states. Same neuron does not respond to the cue's appearance at any brightness in the shuffled condition. Responses to both the 1/3 and 1/2 cues disappeared in the shuffled condition. Time scale at the *bottom right* represents 500 ms, and the response scale at the *bottom right* represents 20 spikes/s.

was very strong when the monkey was performing the task under the cued condition. The monkeys' error rate was low ( $<10\%$ ; see METHODS) when every correctly performed DMS trial was rewarded in the last training period before the schedule was introduced. After the schedule was introduced, the error rates were greatest ( $\sim 20\%$ ) in the trial that was farthest from reward (1/3 schedule state) and lowest ( $\sim 3\%$ ) in the trials

closest to reward (1/1, 2/2, and 3/3 schedule states), suggesting that the monkeys are most motivated during trials in which they know the reward is forthcoming. In short, the monkeys' motivation level in the rewarded trial when they were performing the schedule was even higher than the motivation level when they were performing the task in which every correct trial is rewarded (the training condition).

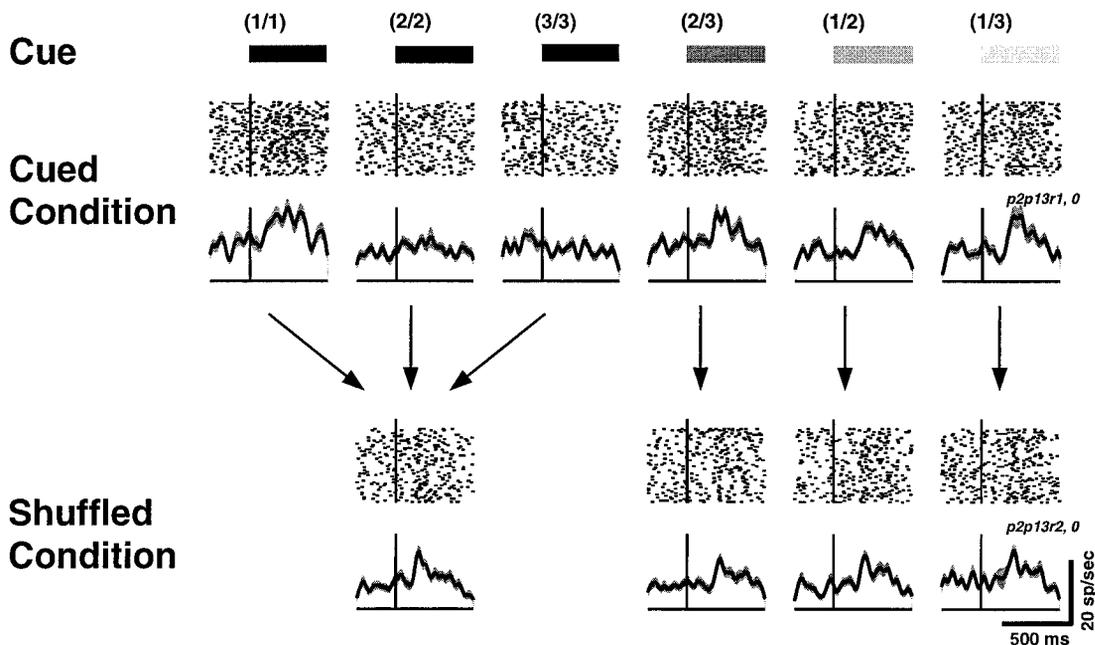


FIG. 16. Cue-related responses of a perirhinal neuron in both the cued and shuffled conditions. Conventions as in Fig. 7. In the cued condition, this neuron responds to the cue's appearance in the 1/1, 1/2, 1/3, and 2/3 schedule states but not in the 2/2 and 3/3 states. In the shuffled condition, the same neuron responds to the cue's appearance in all states, and stops differentiating between the cue's brightnesses (single-factor ANOVA, NS). Time scale at the *bottom right* represents 500 ms, and the response scale at the *bottom right* represents 20 spikes/s.

The cue-related behavior of the monkeys in the visually cued schedule task used here is similar to that seen in earlier studies (Bowman et al. 1996; Shidara et al. 1998). The monkeys performed DMS trials in the present study and color discrimination (red-to-green) trials in those previous studies. Thus the schedule has a large influence on the monkeys' behavior irrespective of the difficulty or complexity of the underlying task (DMS vs. color discrimination).

Intuitively, it seems reasonable to expect the complexity of individual trials also to play a role. The influence of trial complexity is seen by comparing the monkey's behavior in the shuffled condition here to the behavior seen in the shuffled condition by Shidara et al. (1998) (DMS vs. red-to-green color discrimination). In both cases, the monkeys treated the task as one with a variable-ratio reward schedule (constant performance across trials) (Mackintosh 1983). Although the monkeys are performing very well during the shuffled condition here (<10% error), their performance falls significantly short of the best observed (~3%), whereas in the Shidara et al. (1998) study using color discrimination, the monkeys performed at the maximum level (i.e., most quickly and accurately) during the shuffled condition. One possible interpretation is that DMS is more difficult than color discrimination and hence is more aversive in some conditions (e.g., in the shuffled condition). However, under the cued condition, apparently the knowledge that a correct response on the trial will be rewarded overrides the difficulty and/or aversiveness associated with the individual trials. Thus the balance between the appetitive and aversive aspects of individual trials appears to be modulated by both the schedule and the difficulty of the trials.

### Latency

Although the shortest latency for perirhinal neuronal responses is about the same as the shortest latency for TE neuronal responses (cf. Fig. 6), the distribution of latencies for perirhinal neurons shifts from a median of 78 ms in TE to 144 ms in perirhinal cortex, a shift of 66 ms. In area TE the latency has been reported to be 70–120 ms, whereas in perirhinal cortex the latency has been reported to be as short as 100 and averaging 150 ms (Baylis et al. 1987; Nakamura et al. 1994; Richmond et al. 1983, 1987; Xiang and Brown 1998). Xiang and Brown (1998) also found a large latency difference (~70 ms) across these two areas. The latency difference between these two directly connected areas is a striking departure from the general observation that latencies in sequentially connected visual cortical areas shift by 10–15 ms (Baylis et al. 1987; Robinson and Rugg 1988). Not every study has revealed a difference in latency across these two areas (Nakamura et al. 1994).

There are presumably many possible explanations for this shift in latency distribution, including a requirement for feedback to perirhinal cortex via several other stages or a systematically high threshold that only can be overcome by prolonged integration of the input signal. Currently we have no evidence that sheds light on the mechanism responsible for the large delay in the latency of perirhinal neurons.

### Influence of behavioral context

Overall only about one-quarter of the total response variance in these two areas can be related to the experimental factors (at

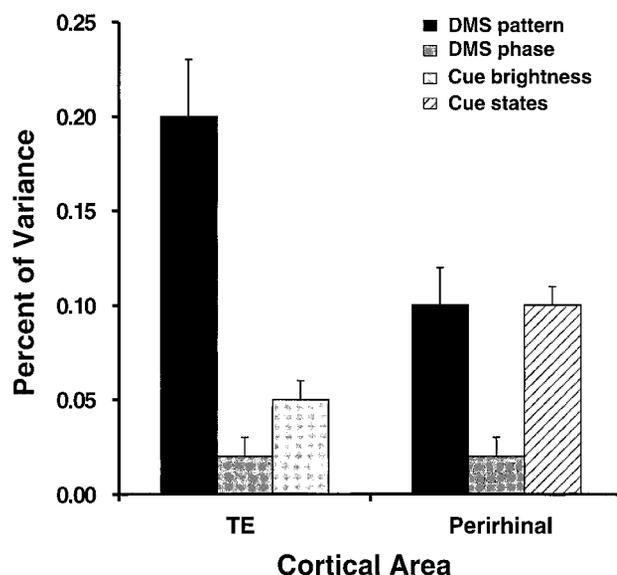


FIG. 17. Percentage of variance in the neuronal response can be explained by various factors. Each bar represents the average contribution of 1 factor to the response variance of either TE or perirhinal neurons. Errors shown are SEs. Distribution of the variance explained by ANOVA is considerably different in area TE than in perirhinal cortex. Variance related to the DMS patterns is larger in TE. Variance related to the cue in TE is the same when related to either the cue's brightnesses or the schedule states (▨). Variance related to the cue is larger in perirhinal cortex, and is largest when related to the 6 schedule states (▩). Also see text and Fig. 11.

least using ANOVA). The variance that is explained is distributed differently across the experimental factors in area TE than in perirhinal cortex (see Fig. 17). The variance related to the DMS patterns is larger (~20%) in TE than in perirhinal cortex (~10%). Furthermore the variance related to the cue is only ~5% in TE, and it is related to the cue's brightness, whereas the variance related to the cue is ~10% in perirhinal cortex when it is interpreted in relation to the cue's schedule states.

It has been shown before and we confirm here that visually elicited responses during DMS show modulations related to the phase of the DMS trial, i.e., the responses are often significantly different in the sample, nonmatch, and match phases (Eskandar et al. 1992; Gross et al. 1979; Li et al. 1993; Miller et al. 1993; Riches et al. 1991). Here we quantify this DMS phase-related modulation and show that although it is significant, it is small. In the only previous study in which the response variance related to the DMS phase was quantified the amount of variance explained by DMS phase was also small (Eskandar et al. 1992). Other studies emphasized response changes that took place as the stimuli became more familiar (Li et al. 1993; Miller et al. 1993; Riches et al. 1991). The response became smaller as the stimuli became more familiar. Here the stimuli were already very familiar, and therefore increasing familiarity should play no part in the small modulations that we report here.

Finally, in area TE the cue-related responses can be regarded as simply sensory driven because TE neurons always fired to the cue's appearance in all schedule states and no extra variance is explained by separating the three end-of-schedule states (1/1, 2/2, and 3/3 states; cf. Fig. 11). The cue-related responses of perirhinal cortex must be regarded as associative and not simply sensory because cue-related responses were differentiable in the three end-of-schedule states (1/1, 2/2, and 3/3

states); in all but two neurons, cue-related responses either disappeared or became indistinguishable in all schedule states under the shuffled condition; and for every neuron, the schedule states account for more variance than cue brightness alone (cf. Fig. 11). Furthermore in perirhinal cortex, the associative effect of the visual cue is as large as the effect related to the DMS patterns. Thus in the conditions used here, it is clear that the physiological properties of perirhinal neurons are distinct from those of TE neurons.

#### *Relation of perirhinal neuronal responses to reward schedules*

The responses of neurons in the anterior part of the temporal lobe (including perirhinal cortex) can be modulated by many factors, such as stimulus identity (Nakamura et al. 1994; Riches et al. 1991) and attention (Desimone 1996; Richmond et al. 1983). Here we found that more than half of the cue-responding perirhinal neurons responded during only a subset of the trials ending different schedules (Table 1) despite the fact that the cue was identical for these trials. Furthermore shuffling eliminated most of the cue-related perirhinal neuronal responses. Thus perirhinal neurons do not specifically code the presence or absence of reward nor what the cue looks like, i.e., its brightness, nor the level of attention directed toward the stimuli. Perirhinal neurons do not respond to bar release or reward delivery as ventral striatum neurons commonly do (Bowman et al. 1996; Schultz et al. 1992; Shidara et al. 1998).

The most parsimonious interpretation of the cue-related responses of perirhinal neurons is that these neurons as a population keep track of progress through these predictable reward schedules. For example, a neuron in class 3 (see Table 1) may signal the beginning of any schedule, a neuron in class 2 may signal the beginning of schedules longer than 1, and the sum of the responses of the two neurons may be used to indicate the one trial in a single trial schedule. Thus perirhinal neurons appear to code the associative meaning of the cue for signaling progress through schedules in a manner similar to the cue-related responses recorded in the ventral striatum by Shidara et al. (1998).

#### *Functional role of perirhinal cortex*

It has been hypothesized that perirhinal cortex is a critical site for consolidation and storage of information about objects (Buckley and Gaffan 1998a–c; Mishkin et al. 1997; Murray et al. 1998; Suzuki 1996). Electrophysiological studies show neurons in the perirhinal cortex respond selectively to complex objects (Nakamura et al. 1994; Riches et al. 1991). Removing the perirhinal cortex produces severe impairment in object recognition memory (Meunier et al. 1993) and in the retention of preoperatively learned object discriminations (Buckley and Gaffan 1997; Gaffan and Murray 1992; Thornton et al. 1997).

An early clue that perirhinal cortex might be related to associative learning came from Spiegler and Mishkin (1981), who reported that removal of both area TE and perirhinal cortex produced impairment in one-trial learning of object-reward associations, suggesting that perirhinal cortex could play a role in attaching associative meaning to objects. More recently, Murray et al. (1993) and Miyashita et al. (1996) showed that monkeys with perirhinal cortex lesions had severe

impairments in visual stimulus-stimulus associations. Other recent work also has shown that the perirhinal cortex is central for other types of stimulus-stimulus association as well (Murray and Bussey 1999). The most recent behavioral and pharmacological studies support the idea that perirhinal cortex is important for associative learning (Herzog and Otto 1998; Murray et al. 1998). In a direct test, we recently have found that rhinal cortex lesions severely impair learning to associate new visual cues with reward schedules of the kind used here (Liu et al. 1999). In light of this behavioral result, our physiological results here support an important role for perirhinal cortex in the development of associative memories and extend earlier behavioral findings by showing that association can involve reward schedules.

#### *Functional difference between TE and perirhinal cortex*

On the basis of anatomic, behavioral and electrophysiological results, the inferior temporal cortical areas are considered to be the end of a stream of visual processing that emphasizes the identity of objects, both their physical appearance and memories related to their identity (Suzuki 1996, Tanaka 1996). Past studies of TE and perirhinal cortex generally have been designed to investigate their role in either object identification or short-term memory of object identity (Suzuki 1996). Neurons in both area TE and perirhinal cortex have shown stimulus selectivity (Desimone et al. 1984; Gross et al. 1972; Nakamura et al. 1994; Riches et al. 1991; Tanaka et al. 1991), and our findings in the DMS trials here are consistent with those findings.

Given how strongly perirhinal neurons code information about the progression of a predictable schedule and given the prominent reciprocal connections between perirhinal cortex and area TE (Saleem and Tanaka 1996; Suzuki and Amaral 1994a), it is surprising that we were only able to detect signals related to the brightness of the cue in area TE. Furthermore, because TE projects directly to perirhinal cortex (Saleem and Tanaka 1996), the transformation from stimulus identity in area TE to stimulus meaning in perirhinal cortex appears to occur in one feedforward processing step. It remains for future work to identify how this transformation can occur.

Although most single-neuronal recording studies have failed to distinguish between TE and perirhinal cortex, Buckley et al. (1997), using selective lesions, found behavioral differences between the two areas. Monkeys with removals of the perirhinal cortex were impaired in performing a short-term memory task but not a color-discrimination task, whereas the monkeys with removals of area TE were deficient in performance on the color-discrimination task but not the short-term memory task. Our results showing that the neuronal responses of perirhinal neurons code the associative behavioral significance of the stimulus lead us to suggest that perirhinal cortex is also critical for associating behavioral meanings with visual stimuli. At this point, we wonder whether unknown associations also could give rise to the perirhinal responses seen in the DMS part of this task. If that was the case, then only one mechanism would be needed to interpret the responses of perirhinal neurons. In support of the speculation, it has been shown that pattern selectivity develops with stimulus-stimulus associations in inferior temporal cortex (Miyashita 1988; Sakai and Miyashita 1991).

Finally, the perirhinal cortex is well-positioned anatomically to contain the signals we have seen. The signals related to the progress of a trial schedule could arise from the connections between perirhinal cortex and areas primarily coding for visual identity such as area TE (Saleem and Tanaka 1997) and areas related to motivation and reward, such as amygdala (Aggleton et al. 1980; Stefanacci et al. 1996; Van Hoesen 1981), ventral striatum (Witter and Groenewegen 1986), and probably the ventral tegmental area (Akil and Lewis 1993, 1994; Insausti et al. 1987). Through these connections, perirhinal cortex may be part of a system including ventral striatum and other areas with reward-related signals gauging the relation between work schedules and rewards.

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